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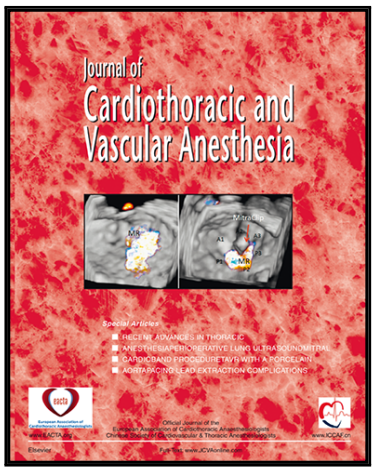

One-year multidisciplinary follow-up of COVID-19 patients requiring invasive mechanical ventilation

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TITLE

One-year multidisciplinary follow-up of COVID-19 patients requiring invasive mechanical ventilation

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ABSTRACT

Objective: Patients with COVID-19 frequently develop acute respiratory distress syndrome (ARDS) requiring intensive care unit (ICU) admission. Data on long-term survival of these patients are lacking. We investigated 1-year survival, quality of life and functional recovery of COVID-19 ARDS patients requiring invasive mechanical ventilation

Design: Prospective observational study

Setting: Tertiary-care university hospital

Participants: All COVID-19 ARDS patients receiving invasive mechanical ventilation and discharged alive from hospital

Interventions: Patients were contacted by phone after 1-year. Functional, cognitive, and psychological outcomes were explored through a questionnaire and assessed using validated scales. Patients were offered the possibility to undergo a follow-up chest CT scan.

Measurements and Main Results: The study included all adult (age ≥ 18 years) patients with COVID-19-related ARDS admitted to an ICU of our institution between February 25th, 2020 - April 27th, 2020), who received at least one day of invasive mechanical ventilation (IMV). Of 116 patients who received IMV, 61 (52.6%) survived to hospital discharge. These survivors were assessed one year after discharge and 56 completed a battery of tests of cognition, activities of daily living and interaction with family members. They had overall good functional recovery, with >80% reporting good recovery and no difficulties in usual activities. A total of 52 (93%) of patients had no

dyspnea at rest. Severe anxiety/depression was reported by five (8.9%) of patients. Comparing 2-months and 1-year data, we observed the most significant improvements in the areas of working status and exertional dyspnea. One-year Chest CT scans were available for 36 patients: fibrotic-like changes were present in four patients.

Conclusions: All patients who survived the acute phase of the COVID-19 disease and were discharged from the hospital were alive at the 1-year follow up and the vast majority of them had good overall recovery and quality of life.

Study Registration: ClinicalTrials.gov NCT04318366

KEY WORDS

coronavirus disease 2019; post-intensive care syndrome; quality of life; acute respiratory distress syndrome; intensive care unit; pulmonary fibrosis; lung recovery

INTRODUCTION

In the first months of 2020, the Coronavirus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread all over the world becoming pandemic, and causing a surge of intensive care unit (ICU) admissions due to severe respiratory failure and acute respiratory distress syndrome (ARDS).[1–4]

Previous studies performed in non-COVID-19 ARDS patients showed that ARDS is frequently associated with long-term functional, psychological and cognitive impairment and reduced quality of life in ICU survivors.[5–8] A similar pattern has been described for other respiratory coronaviruses infections (SARS-CoV-1 and Middle East Respiratory Syndrome [MERS]) as well as for the general ICU population.[9–14]

Short-term mortality rate for COVID-19-related ARDS requiring invasive mechanical ventilation is around 50 %,[3,15]. However, data on long-term mortality and quality of life in this setting are scarce.[16,17] In addition, previous studies showed conflicting data on mid-term recovery, with some studies suggesting an overall reduced quality of life and poor functional recovery[18,19], while other reported an overall good quality of life and better functional recovery as compared with non-COVID-19-related ARDS.[20]

Our group recently published the two months follow-up data of our cohort of invasively ventilated, COVID-19 ICU survivors.[20] Accordingly, we have now performed a 1-year follow-up study of the same cohort to investigate long-term mortality, quality of life, functional and psychological recovery of our patients, as well as computed tomography (CT) characteristics of the lungs.

MATERIALS AND METHODS

Study design and Setting

This study is part of the COVID-BioB study, a prospective observational study performed at ***BLINDED***, a 1,350-bed teaching hospital in Italy. The study was approved by the hospital

Ethics Committee (protocol No. 34/int/2020) and was registered on ClinicalTrials.gov (NCT04318366).[21,22]

Inclusion and exclusion criteria

Details on inclusion and exclusion criteria of our follow-up studies have been previously published.[20,21]

Briefly, this study included all adult (age ≥ 18 years) patients with COVID-19-related ARDS admitted to an ICU of our institution between February 25th, 2020 - April 27th, 2020 (first Italian pandemic wave[23] – see Supplementary Figure 1), who received at least one day of invasive mechanical ventilation (IMV). Of 116 patients who received IMV during the study period, 61 (52.6%) survived to hospital discharge. These survivors were contacted one year after discharge and were given a battery of tests of cognition, activities of daily living and interaction with family members (details on data collection are provided below).

Patients management

Details on hospital organization and patients management in ICU and general wards have been previously published.[4,20–22,24–26] Invasive mechanical ventilation, fluid and pharmacological management of patients were performed according to international guidelines and experts recommendations.[27–31]

Briefly, we aimed for a tidal volume of 6-8 mL/kg of ideal body weight, a driving pressure of ≤ 15 cmH_2O, and a pH > 7.25. Positive end-expiratory pressure (PEEP) was initially set according to the ARDSnet low PEEP/high FiO_2 table, and then individualized according to respiratory system mechanics, hemodynamics and oxygenation. During the first days of ICU stay, we aimed for a slightly negative fluid balance as tolerated by hemodynamics and end-organ function. Rescue treatments including prone positioning, use of neuromuscular blockade, inhaled nitric oxide, and

extracorporeal membrane oxygenation were used as suggested by international guidelines on ARDS management available at that time.[27,31]

Antivirals, adjuvants and immunosuppressants (e.g. steroids) were administered according to clinical judgement and evidence available at that time.[21]

Data collection

Study methodology has been previously described.[20,21]

For this specific 1-year follow-up study, the primary outcome was 1-year survival. We chose survival as primary outcome as this is a strong, clinically relevant outcome and there are no data on 1-year survival of patients with COVID-19-related ARDS who required invasive mechanical ventilation. All other items addressed by the follow-up questionnaire were secondary outcomes.

Baseline demographic and ICU treatment data were collected. For each patient we had at least one telephone number, either belonging to the patient or to a caregiver. The discharged patients were contacted by phone by a trained investigator, and data were progressively recorded in a dedicated database during the phone interview. Firstly, we asked the patient to confirm his/her identity and date of birth, and then we asked further contact details and information about:

- smoking habit at the onset of the disease (current smoker, past smoker > 1 month, never smoker);
- working status at the onset of the disease (actively working or not);
- working status at the time of the call (back to previous job, working with different tasks due to the disease, not working for disease dependent reasons, previously unemployed or retired);
- schooling (none, primary school, middle school, high school, Bachelor's Degree, Master's Degree);
- dysosmia and dysgeusia, either before the onset of the disease and after discharge;
- discrimination that they (or their families) may have endured because of the disease, including denied access to non-urgent care. After that, we administered a telephone assessment

composed of various items, in order to explore multidimensional outcomes. The questionnaire was the same used for the 2-months follow-up,[20] and items are described in details below and in the Supplementary Appendix. Finally, a chest CT scan was offered to all patients. Data were progressively recorded in a dedicated database during the phone interview.

Quality of life evaluation

Multidimensional outcomes were evaluated following our previous protocol.[20] We explored physical recovery and disability via the Glasgow Outcome Scale extended (GOSe),[32,33] the autonomy in walking via the Functional Ambulation Classification (FAC),[34] the dyspnea (either at rest and during an effort such as two floors of stairs) via the Borg Category Ratio 10 (CR-10) scale,[35,36] and the nutritional status via the Mini Nutritional Assessment – Short Form (MNA-SF).[37] The Euro Quality 5 Dimensions 3 Levels (EQ-5D-3L),[38,39] that includes an overall score self-evaluated by the patient, the Visual Analogue Scale (VAS), was used to assess quality of life. We used the Hospital Anxiety and Depression Scale (HADS),[40,41] the PTSD Checklist for DSM-5 (PCL-5 - which assesses the PTSD),[42–44] and the Insomnia Severity Index (ISI)[45] to assess psychological outcomes. We used the Italian Telephonic version of the Mini Mental State Examination (Itel-MMSE) to assess cognitive status.[46]

Chest CT scans

All CT examinations were performed on a 64-row multidetector CT scanner (SOMATOM Definition Flash Dual Source CT, Siemens Healthcare). CT protocol included an unenhanced, breath-hold axial scans of the thorax (from lung apex to the lowest hemidiaphragm); if any concern existed about *air trapping*,[47] an expiratory scan was also performed.

Two experienced radiologists, both blinded to patients' eventual symptoms, independently reviewed all CT images for fibrotic-like changes (*honeycombing*, reticulation and traction bronchiectasis);[47] differences in assessment were resolved with consensus.

Imaging post processing was carried out with commercially available software (Intellispace version 8.0, Philips Medical Systems, *Chronic Obstructive Pulmonary Disease* tool); after automated identification of pulmonary lobes on lung parenchyma windowed slices, the software estimated total lung volume (expressed as cubic centimetre [cc]) and also differentiated diverse areas of lung parenchyma based on Hounsfield Unit (HU) thresholds. To quantify and differentiate between normal and pathologic lung parenchyma, a -740 HU threshold was set: areas with higher-density values were considered pathologic (residual lung damage, expressed as percentage of the whole lungs volume).[48]

One-year follow-up imaging was compared to chest CT scans of the same patients acquired three months after ICU discharge. Accordingly, any change in the burden of residual lung damage was noted.

Statistical analysis

Statistical analysis was performed using Stata 16 (StataCorp. 2016. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP). Data were presented as medians with interquartile range (IQR: 25th – 75th percentiles) or as means with standard deviation (SD). Means and SD were used with normally distributed variables, while medians and IQR were used with non-normally distributed variables. Categorical and dichotomous variables were presented as absolute number and percentages (%). No data imputation for missing data was performed.

We compared questionnaire data obtained at 2-months and CT scan at 3-months with the same data collected at 1-year. Dichotomous variable were compared using chi-square test or Fisher's exact test, while continuous variables were compared using Student's t-test or Wilcoxon sum-rank test as appropriate.

We compared baseline characteristics and treatment data patients with a good overall recovery (defined as Glasgow Outcome Scale extended of 7 or greater) and patients with persistent disability. Data were compared among the groups using Fisher exact tests or Wilcoxon rank-sum tests. We

included variables with a p-value of less than 0.05 at univariate analysis in a multiple logistic regression model to predict good 1-year functional outcome. Collinearity and overfitting were assessed using a stepwise regression model and Pearson correlation test. In the multiple logistic regression analyses, we expressed clinical factors or potential confounding variables as odds ratio (OR) with 95% confidence interval (CI). A p-value < 0.05 was considered significant.

A convenience sample was chosen for this preliminary observational study. A post-hoc power calculation considering a 1-year post-ICU-discharge mortality for ARDS patients of 10%[8] and an alpha of 0.05 showed that the study has a power of 80.5%.

RESULTS

Baseline characteristics of patients and ICU course

Overall, a total of 116 COVID-19-related ARDS patients were admitted to an ICU at our institution and received invasive mechanical ventilation (Figure 1). Of these, 61 patients (52.6%) were discharged alive from the hospital. No patient was lost to 1-year follow-up and all patients discharged from hospital were alive (1-year survival rate 61/61 [100%]). Five patients refused to respond to 1-year follow-up questionnaire (questionnaire response rate 56/61 [91.8%]) (Figure 1).

Detailed baseline characteristics and general ICU course of the 56 patients included in the study are presented in Table 1, while data on specific medical therapies received are presented in Supplementary Table 1. Patients were prevalently males (89%) and were 56 ± 11.9 years old.

The overall quality of life assessed through the EQ-5D-3L test showed that the vast majority of patients had no difficulty in walking (82%), self-care (95%), or usual activities (84%). A total of five patients (8.9%) reported severe anxiety/depression (Table 2).

At 1-year follow-up, psychological tests confirmed low rates of anxiety, depression, PTSD, insomnia and cognitive impairment (Table 2).

Six patients (11% of the total number and 16% of those able to work at baseline) reported not being able to work due disease-dependent reason (Table 2).

A total of 45/56 patients (80.3%) reported good recovery as defined by the GOSe. Similarly, 93% of patients had no dyspnea at rest, while 16/56 (28.5%) reported exertional dyspnea (ranging from "light" to "very strong"). A total of 50 patients (89%) reported to walk independently anywhere. The MNA-SF showed that 19/56 patients (33.9%) were malnourished or at risk for malnutrition (Table 3).

Episodes of reported personal or family discrimination due to their COVID-19 illness were reported by four (7.1%) and four (7.1%) of patients, respectively (Table 2).

Alterations in smell and taste were present before ICU admission in five (8.9%) and five (8.9%) patients, respectively, and persisted after hospital discharge in four (7.1%) and four (7.1%) patients (Table 2).

Comparison between questionnaire results obtained at 2-months and 1-year follow-up are presented in Supplementary Tables 2 and 3. A total of 35 patients responded to both follow-ups and were included in this analysis. Overall, we observed the most significant improvements in the areas of working status, exertional dyspnea, nutrition status, and recovery according to GOSe. On the contrary, we observed limited improvement in quality of life as assessed by EQ-5D-3L questionnaire, in cognitive and psychological outcomes, and in the functional ambulation classification.

Overall recovery expressed as GOSe was not different among those who were hospitalized for less two months (N=41) as compared with those hospitalized longer than two months (N=13) (median GOSe 8 (7-8) versus 8 (7-8), respectively, p = 0.61, with data available for 54 patients).

Chest CT scans

A total of 36 patients (64.3%) underwent one-year follow-up chest CT scan. Of these, 29/36 (80.5%) already had a previous follow-up chest CT scan three months after ICU discharge, and were subsequently enrolled in this analysis.

Qualitative assessment – Three months after ICU discharge, eight patients (27.6%) had a fibrotic-like CT pattern; at one-year follow-up, four patients only (13.8%) kept fibrotic-like changes.

Quantitative assessment – Quantitative CT features are summarized in Table 4. At 1-year follow-up, the median residual lung damage was 7.6% (5.6-10.7) vs. 17.3% (12.1-23.1) three months after ICU discharge. Between these two time points, total lung volume demonstrated a median increase of 925 cc (318-1194) (Supplementary Table 4).

An example of chest CT findings over time is presented in Supplementary Figure 2.

Predictors of good overall recovery at 1-year

Results of univariate and multiple logistic regression analysis to assess predictors of good 1-year overall recovery are presented in the Supplementary Tables 5 and 6.

Multiple logistic regression analysis identified having few comorbidities as the only independent predictor of good overall 1-year recovery (OR = 0.18; 95% CI = 0.04 to 0.78; p = 0.023).

DISCUSSION

Key findings

In this observational study, we found that 1-year mortality for COVID-19-related ARDS requiring invasive mechanical ventilation is low in patients who survive the initial hospitalization. In addition, we found that, at 1-year follow-up, the majority of patients were free of symptoms. Finally, follow-up chest CT scans showed significant, progressive regression of residual lung damage, with low prevalence of pulmonary fibrotic-like changes.

Relationship to previous studies

Previous studies in COVID-19 patients generally reported follow-up limited to four to six months after critical illness,[18,19,49–52] with limited long-term data available. A small study including 23 patients reported a 1-year survival rate of 57%, consistent with our findings.[17]

Collectively, follow-up studies investigating short-term recovery after critical COVID-19 showed a significant burden of functional limitations and psychological sequelae in ICU survivors, but with gradual improvement over the period from discharge to six months.[50,52]

In the largest study, Morin et al. assessed four-months respiratory, cognitive, and functional outcomes in 478 COVID-19 patients, including 142 who had been admitted to the ICU and 73 intubated patients.[19] In their study, the Authors used different scales but dyspnea was reported in 34% of intubated patients, somewhat higher than our 28% of exertional dyspnea. Similarly to our study, anxiety or depression were present in about 25% of patients, and fibrotic changes were observed in 20% of patients. Unfortunately, the Authors did not present information on post-ICU discharge survival, although the overall mortality after hospitalization was 12% in their cohort

Other studies showed a relatively low post-discharge mortality, similar to our study, with variable rates of radiological, functional and psychological recovery.[18,50,51]

Interestingly, in contrast to previous publications,[8,51] we found that age, duration of ICU stay and mechanical ventilation were not independently associated with 1-year outcome, while we identified baseline comorbidities as a key risk factor. However, these findings may be simply due to different definitions of good outcome and different length of follow-ups.

However, heterogeneity of previous studies in terms of enrolled patient population (hospitalized/non hospitalized, critically ill/non critically ill, ventilated/non ventilated patients), the different time point of the follow up (the majority of the studies had shorter follow up), and the different metrics adopted by researchers to assess the outcomes, makes our findings only partially comparable with previous literature.

Comparison with non-COVID-19-related ARDS is difficult due to frequent use of different scale to assess quality of life and recovery. Interestingly, we observed a higher post-discharge survival as compared with non-COVID-19-related ARDS, where post-ICU mortality has been reported to be as high as 11%.[8]

However, available studies collectively showed reduced quality of life, functional recovery, and several psychological sequelae, with a relatively high prevalence of post-traumatic stress disorder.[5,7,53–55] Our data, together with data from other studies, suggest that recovery from critical COVID-19-related ARDS is somewhat better than for non-COVID-19-related ARDS, although studies providing direct comparison between these two populations are lacking.

Interestingly, on that note, we observed a median residual lung damage at 1-year follow-up of 7.6%, slightly lower when compared with previous reports concerning non-COVID-19-related ARDS, reporting a residual lung damage involving 10 to 25% of lung parenchyma.[56]

Implications of study findings

Our study, together with data from literature, suggest that, in COVID-19-related ARDS patients, mortality after ICU discharge is low and long-term recovery is overall good. In particular, clinical findings are consistent with radiological findings obtained through follow-up chest CT scans. Therefore, our data underline that clinicians caring for COVID-19 patients, and in particular for those admitted to an ICU, should be reassured that patients surviving the acute phase will have a good functional recovery after one year. Of course, our data should be interpreted considering that ICU mortality of COVID-19-related ARDS patients is approximately 50%.[15] Furthermore, our study suggests that post-ICU multidisciplinary follow-up for critically ill patients may have an important role for long-term outcomes.[14,57]

The CDC (Centers for Disease Control and Prevention), together with the US Department of Human Health Services, rise the attention over the post-COVID conditions, now classified as a disease according to the Americans with Disabilities Act (ADA).[58] This post-viral syndrome, is defined as “persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms”.[59] Inside this syndrome, two further categories exists: the subacute or ongoing symptomatic COVID-19 (between weeks 4 and 12 beyond acute infection), and chronic or post-COVID-19 syndrome (beyond 12 weeks from acute infection). Several hypothesis have been

made to explain the long-COVID, and as well as for the post-intensive care syndrome its pathophysiology is probably multifactorial: an excessive inflammatory response, the persistence of the virus in certain reservoir tissues, the immune dysregulation leading to reactivation of pathogens, the role of the host microbiome, coagulation and clotting abnormalities, autoimmunity, and a direct role of the virus.[60] Inside this complex disease, we found a relatively low prevalence of neurologic impairment at 1-year as compared with previous literature and studies with shorter follow-up.[61] Indeed, among COVID-19 survivors, anxiety, depression, sleep disturbance and PTSD were reported up to 30-40%.[59], although prevalence of these disturbances is highly variable across studies.[62]It is possible that the relatively young age of our patients and the prevalence of males,[63] led to better recovery from critical illness. Furthermore, symptoms of post-intensive care syndrome have been shown to improve over time[14], and is possible that our dedicated post-COVID-19 follow-up clinic helped in subsequent recovery.[57,64,65] Notably, in a 6-month post discharge assessment of COVID-19 patients, female, compared to men, were found to have an OR 2.22 (95% CI 1.24-3.89) for pulmonary diffusion impairment, an OR 1.8 (CI 1.39-2.34) for anxiety and depression, an OR 1.33 (CI 1.05-1.67) for fatigue and muscle weakness.[63] Indeed, female sex was confirmed in several publication to be a risk factor for long-term psychologic/psychiatric sequalae,[62] and several studies confirmed improvement of symptoms over time also after COVID-19-related ARDS.[62]

Notably, our data were collected at the beginning of the COVID-19 pandemic, thus before delta variant became prevalent. In particular, the first case of delta variant in Italy was registered in April 2021, one year after the admission in the ICU of our last patient. Our data may therefore not apply to delta variant patients.

Our study confirms radiological data from previous studies, which reported unexpected low prevalence of fibrotic-like changes at short-term follow-up,[19,50,66] and also provides new insights suggesting reversal of these changes and further lung healing after one year. A possible explanation could lie in the previously proposed virus-induced lung frailty, which is thought to be a main contributor for the high incidence of barotrauma in COVID-19 patients.[67,68] In this prospective, the

honeycombing CT pattern, when present, could represent a subpleural cluster of small pneumatoceles rather than cystic air spaces resulting from irreversible lobular disruption. Furthermore, residual lung damage does not necessarily correspond to lung fibrosis, which instead has a strict radiological definition.[47]

Finally, a relevant proportion of our patients received hydroxychloroquine as adjuvant antiviral therapy. Notably, following publication of several randomized trials showing negative results,[69] use of hydroxychloroquine as treatment for COVID-19 greatly decreased and is no longer recommended. Although we cannot exclude that use of the drug contributed to the good long-term outcome, this seems unlikely given the negative results of major randomized on its use.

Strengths and limitations of the study

This is the first study presenting clinical and radiological 1-year follow-up data for patients with COVID-19-related ARDS . A strength of our study is the absence of "lost-to-follow-up" patients and the almost complete questionnaire follow-up. Furthermore, we employed several previously validated scales to assess functional, psychological and cognitive outcomes. Finally, the presence of quantitative radiological data represents major strength of the present study

The study is limited by its single-center design, by the small sample size, and by absence of a control, non-COVID-19-related ARDS group and non-invasively ventilated COVID-19 patients. However, obtaining a control group of a comparable during the same time this was almost impossible due to the overwhelming number of COVID-19 cases. The present study focused only on patients who received invasive mechanical ventilation (i.e. the most severely ill patients) while the long term outcome of patients treated with non-invasive ventilation is currently under investigation.[24,70,71]

Patients included in our study were relatively young, prevalently male, with normal BMI and few comorbidities. Older patients with greater burden of comorbidities were less likely to be admitted to ICU during pandemic crisis[24,71], and had higher risk of death. Therefore, our data may suffer from

selection, gender and survival bias.[3,15] However, age range of patients admitted to our ICUs is comparable to that of patients admitted to ICUs in the whole Lombardy region during the same period, [3,15] and a male prevalence of our ICU and hospitalized patients was already known.[72]

We did not collect data on long-term occurrence rate of cardiovascular and thrombotic events, or long-term organ function (e.g. renal function or pulmonary function tests). However, investigation of these outcomes was not among the objectives of this study and is currently subject of separate investigations.[73]

The study is not randomized, so we can't determine whether referral of patients to our post-COVID follow-up clinic[57] has influenced long-term outcome.

Future studies and prospects

Future studies should confirm in a larger sample size our findings of a low post-discharge mortality and good functional and radiological recovery following COVID-19-related ARDS. In addition, the role of post-ICU follow-up clinics, as well as multidisciplinary long-term management protocols should be assessed and defined.

Finally, future studies should further define the correlation between pathogenesis of COVID-19 lung damage, acute-phase treatments, and long-term lung fibrosis.

Conclusions

Our study suggests that, among ICU patients with COVID-19-related ARDS who required invasive mechanical ventilation and were discharged alive from hospital (approximately 50% of ICU COVID-19-related ARDS patients receiving invasive ventilation), 1-year survival is high. Furthermore, overall recovery and quality of life of survivors are good after 1-year. Radiological findings are consistent with clinical findings, showing a progressive reduction in residual lung damage. Recovery seems better than for non-COVID-19-related ARDS, although a direct comparison is lacking.

CONFLICT OF INTEREST

None

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None

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FIGURE LEGENDS

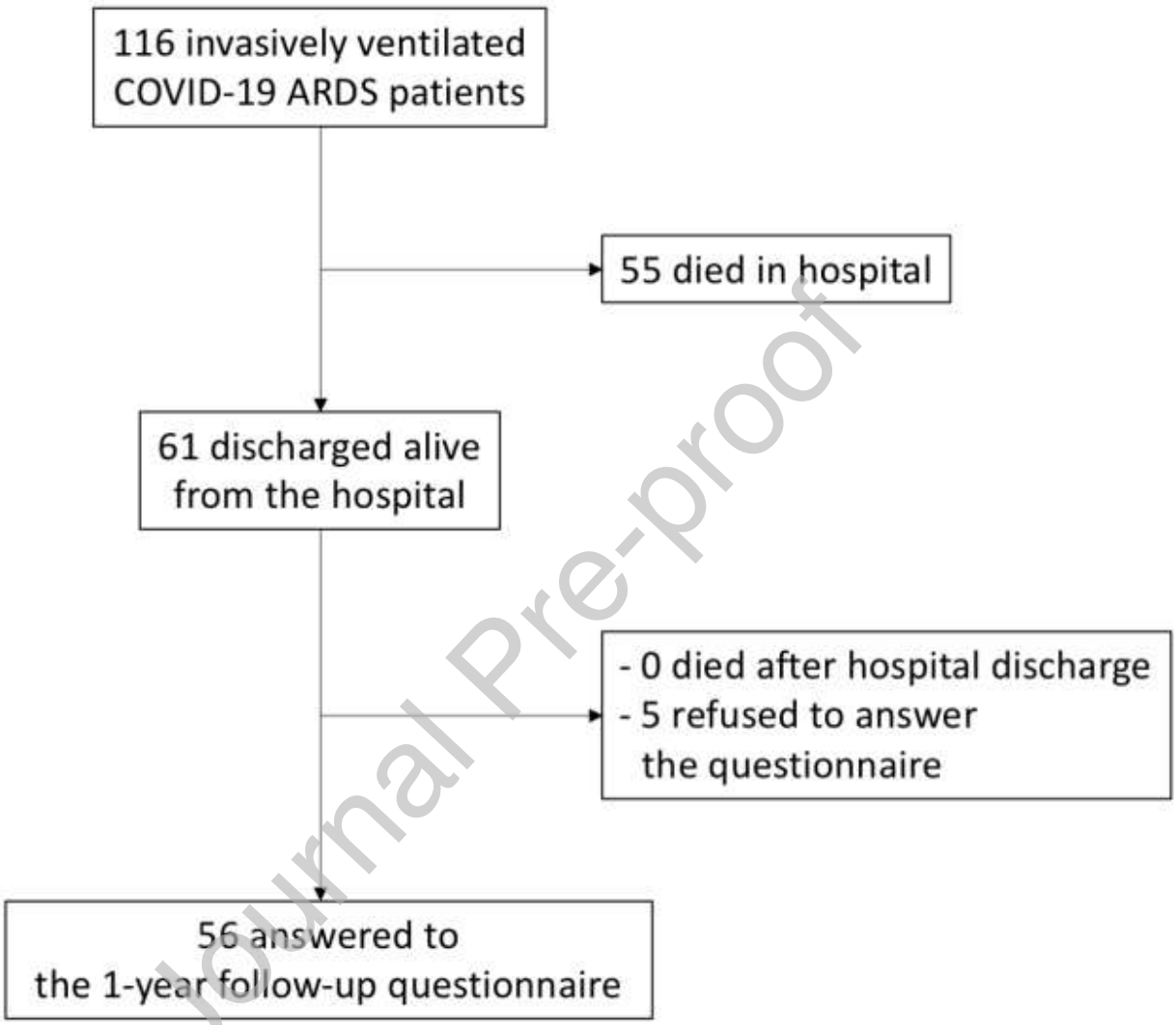

Figure 1. Flow diagram showing the screening to follow-up.

Table 1 - Characteristics of the 56 invasively ventilated COVID-19 ARDS ICU patients who were discharged home and replied to the 1-year follow-up questionnaire

Baseline characteristics	**Value** **N: 56**	**N° of missing values**
Age (years), mean ± SD	56±11.9	-
Male sex, no. (%)	50 (89%)	-
BMI (kg/m^2), mean ± SD	23.6±10.4	10
PaO_2/FiO_2 at ICU admission, mean ± SD (mmHg)	120±50.8	2
ARDS severity at evaluation (according to Berlin criteria)		2
- Mild, no. (%)	5 (9.3%)	
- Moderate, no. (%)	26 (48%)	
- Severe, no. (%)	23 (43%)	
Comorbidities		6
- 0, no. (%)	27 (48%)	
- 1, no. (%)	23 (41%)	
- 2, no. (%)	3 (5.4%)	
- > 3, no. (%)	3 (5.4%)	
Schooling		22
- Primary school, no. (%)	3 (8.8%)	
- Middle school, no. (%)	11 (32%)	
- High school, no. (%)	12 (35%)	
- Bachelor's Degree, no. (%)	3 (8.8%)	
- Master's Degree, no. (%)	4 (12%)	
- None, no. (%)	1 (2.9%)	
Working status		1
- Working, no. (%)	31 (56%)	

- Unemployed or retired, no. (%)	24 (44%)	
Smoking status		
- Never, no. (%)	36 (64%)	
- Current smoker, no. (%)	3 (5.4%)	
- Former smoker > 1 month, no. (%)	17 (30%)	
During ICU stay		
CRRT, no. (%)	9 (16%)	-
Tracheostomy, no. (%)	15 (27%)	-
Prone positioning, no. (%)	40 (72%)	3
Inotropic support/vasopressors, no. (%)	46 (87%)	3
ECMO, no. (%)	3 (5.4%)	-
Neuromuscular Blocking agents, no. (%)	47 (89%)	3
Days in hospital before ICU admission, median (IQR)	3 (0-5)	2
Length of mechanical ventilation, median (IQR)	11.5 (7-19)	2
Length of ICU stay, median (IQR)	13 (9-21)	2
Length of Overall hospital stay, median (IQR)	30 (23-44)	7
Days from ICU discharge to follow-up, median (IQR)	349 (343-356)	2

BMI: body mass index; CRRT: continuous renal-replacement therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range; PaO_2/FiO_2: arterial partial pressure of oxygen to fraction of inspired oxygen ratio

Table 2 - Quality of life, psychological, cognitive, and miscellaneous outcomes of 56 invasively ventilated COVID-19 ARDS ICU patients - 1 year follow-up

Items	Value N: 56	N° of missing values
Euro Quality 5 Dimensions 3 Levels (EQ5D3L) - mobility		-
- No difficulty to walk, no. (%)	46 (82%)	
- Mild difficulty to walk, no. (%)	1 (1.8%)	
- Moderate difficulty to walk, no. (%)	7 (13%)	
- Unable to walk, no. (%)	2 (3.6%)	
Euro Quality 5 Dimensions 3 Levels (EQ5D3L) –self- care		-
- No difficulty to wash or dress, no. (%)	53 (95%)	
- Mild difficulty to wash or dress, no. (%)	1 (1.8%)	
- Moderate difficulty to wash or dress, no. (%)	2 (3.6%)	
Euro Quality 5 Dimensions 3 Levels (EQ5D3L) –usual activities		-
- No difficulties in usual activities, no. (%)	47 (84%)	
- Mild difficulties in usual activities, no. (%)	1 (1.8%)	
- Moderate difficulties in usual activities, no. (%)	6 (11%)	
- Not able in usual activities, no. (%)	2 (3.6%)	
Euro Quality 5 Dimensions 3 Levels (EQ5D3L) –pain or discomfort		-
- No pain or discomfort, no. (%)	34 (61%)	
- Light pain/discomfort, no. (%)	2 (3.6%)	
- Moderate pain/discomfort, no. (%)	17 (30%)	
- High pain/discomfort, no. (%)	3 (5.4%)	
Euro Quality 5 Dimensions 3 Levels (EQ5D3L) –anxiety and depression		-
- Not anxious/depressed, no. (%)	36 (64%)	

- Moderately anxious/depressed, no. (%)	15 (27%)	
- Severely anxious/depressed, no. (%)	5 (8.9%)	
Visual Analogue Scale (VAS) for self-perceived health state, mean ± SD	76±18.7	-
Hospital Anxiety and Depression Scale (HADS) –anxiety, median (IQR)	3 (1-6)	2
Hospital Anxiety and Depression Scale (HADS) –depression, median (IQR)	2 (0-5)	2
Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5), median (IQR)	7 (2-15)	2
Insomnia Severity Index (ISI), median (IQR)	0 (0-4)	1
Italian telephone Mini Mental State - Examination (I-tel MMSE), median (IQR)	22 (22-22)	1
Working status		1
- Working, no. (%)	31 (56%)	
- Previously unemployed or retired, no. (%)	18 (33%)	
- Working with different tasks due to disease, no. (%)	-	
- Not working for disease DEPENDENT reasons, no. (%)	6 (11%)	
Alteration in smell Before ICU, no. (%)	5 (8.9%)	
Persisting after 1 year, no. (%)	4 (7.1%)	
Alteration in taste Before ICU, no. (%)	5 (8.9%)	
Persisting after 1 year, no. (%)	4 (7.1%)	
Discrimination due to the disease –Personal–at least one episode, no (%)	4 (7.1%)	
None, no. (%)	52 (93%)	
Discrimination due to the disease –Family–at least one episode, no. (%)	4 (7.1%)	
None, no. (%)	52 (93%)	
Denied access to non-urgent care, no. (%)	3 (5.4%)	

ICU: intensive care unit; IQR: interquartile range

Table 3 - Functional outcomes of 56 invasively ventilated COVID-19 ARDS ICU patients - 1 year follow-up

Items	Value N: 56	N° of missing value
Glasgow Outcome Scale extended (GOSe)		-
- Upper good recovery, no. (%)	36 (64%)	
- Lower good recovery, no. (%)	9 (16%)	
- Upper Moderate Disability, no. (%)	6 (11%)	
- Lower Moderate Disability, no. (%)	2 (3.6%)	
- Upper Severe Disability, no. (%)	1 (1.8%)	
- Lower severe disability, no. (%)	2 (3.6%)	
Dyspnea at rest (Borg Category Ratio 10 scale)		
- Nothing at all, no. (%)	52 (93%)	
- Light, no. (%)	1 (1.8%)	
- Moderate, no. (%)	1 (1.8%)	
- Strong, no. (%)	1 (1.8%)	
- Very strong, no. (%)	1 (1.8%)	
Exertional Dyspnea (Borg Category Ratio 10 scale)		-
- Nothing at all, no. (%)	30 (54%)	
- Very very slight, no. (%)	8 (14%)	
- Very slight, no. (%)	2 (3.6%)	
- Slight, no. (%)	8 (14%)	
- Moderate, no. (%)	2 (3.6%)	
- Somewhat intense, no. (%)	1(1.8%)	
- Intense, no. (%)	2 (3.6%)	
- Severe, no. (%)	1 (1.8%)	

- Very severe, no. (%)	2 (3.6%)
Mini Nutritional Assessment –Short Form (MNA-SF)	-
- 0- 7 points (malnourished), no. (%)	5 (8.9%)
- 8- 11 points (at risk for malnutrition), no. (%)	14 (24%)
- 12- 14 points (normal nutritional state), no. (%)	37 (67%)
Functional Ambulation Classification (FAC)	
- Can walk independently anywhere, no. (%)	50 (89%)
- Requires help on stairs, slopes or uneven surfaces, no. (%)	2 (3.6%)
- Need continuous or intermittent support, no. (%)	2 (3.6%)
- Need firm continuous support, no. (%)	1 (1.8%)
- Can not walk, no. (%)	1 (1.8%)

Table 4 - Quantitative assessment of residual lung damage and total lung volume at both time points (three months and one year follow-up).

	Residual Disease Burden (%)		
	Three months follow-up	***One year follow-up***	***Median decrease***
Both lungs	17 (12.1 – 23.1)	7.6 (5.5 – 10.7)	9.9 (4.9 – 15.1)
Right lung	18 (11.5 – 21. 7)	7.9 (5.5 – 9.8)	9.8 (3.6 – 14.2)
Left lung	18 (10.3 – 28.6)	8.2 (5.5 – 11.8)	10.4 (3.1 – 15.3)
Right upper lobe	15 (10.3 – 21.9)	6.9 (5.2 – 10.1)	8 (3.9 – 14.8)
Right middle lobe	8.1 (5.3 – 16.3)	4.5 (2.7 – 8.5)	3.8 (1 – 7.22)
Right lower lobe	21 (12.8 – 27.1)	8.6 (5.7 – 12.6)	10.1 (5.7 – 17.9)
Left upper lobe	13.7 (9.5 – 20.8)	6.6 (4.7 – 11.6)	7.0 (3.1 – 11.8)
Left lower lobe	23.1 (10.7 – 30.4)	8.5 (5.9 – 13.4)	12.5 (4.1 – 18,1)